DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

JAN 6 2004

The Honorable Jim Kolbe
House of Representatives
Washington, D.C. 20515

Dear Mr. Kolbe:

Thank you for your letter supporting the Arizona Department of Health Services' (ADHS) request for additional assistance from the Centers for Disease Control and Prevention (CDC) in addressing the community's concerns about a cancer cluster in Sierra Vista, Arizona.

Please be assured that I am aware of the importance of working with ADHS to answer the citizens' health questions concerning their leukemia cluster. We have been in contact with ADHS for more than a year and have attempted to provide assistance in a timely and helpful manner. During this time, CDC staff traveled to Arizona and collaborated with ADHS staff on the following issues:

- During a meeting in Phoenix on October 24 and October 25, 2003, we discussed the apparent increase in leukemia incidence and the scientific approaches to investigating leukemia clusters.
- Since that initial meeting, CDC and ADHS have participated in several conference calls to discuss technical issues concerning scientific approaches to leukemia cluster investigations.
- CDC provided ADHS with the entire report on the Churchill County childhood leukemia study, including follow-up investigation reports, and methodology including protocols and questionnaires.
- CDC offered to collect, analyze, and bank biological samples from the Sierra Vista children with leukemia. ADHS has taken this offer under advisement.

On October 31, 2003, Dr. Timothy Flood with the ADHS Cancer Registry e-mailed CDC requesting the agency to respond to several questions posed by ADHS. The questions were carefully considered by many scientists and then forwarded through the CDC National Center for Environmental Health (NCEH) clearance process to ensure that scientifically accurate and sound guidance was provided to ADHS. Enclosed for your information are the ADHS questions and NCEH's answers, which were forwarded to Dr. Flood.

During the past 2 years, CDC has surveyed all state health departments concerning their needs in the area of cancer clusters. Our recent activities in addressing these stated needs include the following:

- Designing and implementing a uniform CDC inquiry system to address cancer cluster inquiries by e-mail (EHHEinq@cdc.gov) or telephone (1-888-232-6789 or 404-498-1453).
- Designing and enriching the CDC/NCEH cluster website which may be accessed at www.cdc.gov/nceh/clusters.
- Conducting a review of state protocols on cancer cluster inquiry and investigation at the state level and returning individualized reports to each state.
- Reviewing and describing media coverage of cancer cluster reports in the United States, 1997-2001.
- Visiting multiple states with recent cancer cluster investigation experience.
- Convening two workshops on cancer cluster protocol among states.
- Creating/facilitating a CDC-sponsored electronic cancer cluster listserv to enhance communication among states.

CDC will continue to work closely with ADHS and support their efforts in analyses, biological samples, health education, and communication to address the cancer cluster in Sierra Vista. Thank you, again, for your interest in this matter. Should you need additional information, please feel free to contact me directly.

Sincerely,

Julie Louise Gerberding, M.D., M.P.H.
Director

Enclosure

National Center for Environmental Health (NCEH) Report to the Arizona Department of Health Services on Childhood Leukemia in Sierra Vista

On October 31, the Arizona Department of Health Services (ADHS) requested consultation from the Centers for Disease Control and Prevention (CDC) on scientific issues related to ADHS' investigation of leukemia cases in Sierra Vista, Arizona. The following is the report prepared by CDC's Division of Environmental Hazards and Health Effects, NCEH, in response to the questions posed by ADHS.

Questiona About Rates:

1. **Do experts in leukemia (oncologists, epidemiologists, geneticists, pathologists) think that the various subtypes (e.g., AML, ALL) have differing causes? Should ADHS calculate leukemia rates according to subtype?**

The science currently available concerning the etiology of childhood leukemia is not complete although there is evidence linking certain specific exposures to the development of leukemia, notably ionizing radiation, benzene, and some genetic syndromes. Exposure to benzene and ionizing radiation increases the risk for development of both ALL and AML, possibly to differing extents. These are likely common etiological factors. In terms of calculation of leukemia rates, it is standard practice to calculate rates of leukemia separately for each subtype (cases per 100,000). However, if it is believed that these cases of leukemia (both ALL and AML) might be related to a common risk factor, one might suggest looking at the rates combined as well. Thus, in the initial stages of the investigation, since there is the possibility of common etiology, the rates should be looked at separately as well as together.

In the study of Childhood Leukemia in Churchill County, Nevada, cases of AML and ALL were initially considered as a combined rate for childhood leukemia. During data analysis, we considered all cases combined as well as stratifying by subtypes and cell types.

2. **Possible fluctuating populations in Sierra Vista could add uncertainty about the estimates of the true denominator. Are there specific denominator issues over which Arizona should be concerned (We are aware of the Fallon document titled, *Expert Panel's Recommendations, Appendix 1*, that addresses population dynamics)?**

In many studies, the choice of appropriate denominator can be debated. The denominator obviously should reflect the population from which the cases came, or the susceptible population. The question of where to draw boundaries is, as you are aware, dependent on several factors specific to the area in question. As to these issues specific to Arizona,

probably a multidisciplinary group of Arizona scientists would best be able to determine the appropriate denominator.

In the Review and Recommendations of the Expert Panel, February 15, 2001, the recommendation was made to the Nevada Health Division that the characteristics and time course of population movement into the Fallon area for the period 1999-2000 be investigated. The panel recommended collecting demographic data on changes in the population of Fallon, particularly looking for evidence of migration of new long-term residents into the community during this time period. To the best of our knowledge, this was not done in Fallon. This would be a challenging task which might yield results that are difficult to interpret.

Questions About Causes:

3. Do the findings in Fallon direct us to look at specific environmental factors in Sierra Vista?

In terms of any related findings from the Fallon, Nevada, study, none of the results of tests on biologic or environmental samples suggested a link between an environmental exposure and increased risk of leukemia. In the report that you provided, *Health Consultation: Review of Environmental Data in Air, Drinking Water and Soil,* etiologic agents that have shown a relation to leukemia and other cancers were addressed. It appears that the exposures under consideration were assessed adequately, and no common environmental exposures from drinking water, ambient air, or waste sites were identified that might have placed the residents of Sierra Vista at greater risk of developing leukemia.

4. Military towns are notorious for high, population turnover. Is "population-mixing" a theory worthy of consideration as a cause of leukemia in Sierra Vista?

The Expert Panel, which convened for the study of leukemia in Fallon, Nevada, considered the possibility that the elevated rate of ALL might be due to an unusual mixing of people, as might occur in a relatively isolated rural area such as Churchill County. Population-mixing theory suggests that exposure to a variety of infectious agents (viral and bacterial) may trigger an unusual and rare reaction that affects a very small number of children within the susceptible population. The hypothesis suggests that ALL is not infectious, spreading from one person to another, but an unusual complication to a common infection within a susceptible population. CDC has begun a study examining DNA from study participants to determine if there are differences among genes that may affect susceptibility to leukemia. The Expert Panel suggested that this theory deserved further examination and also might be tested by calculating rates of ALL in other rural areas of the United States with population-mixing factors in operation. The exposure assessment study that was conducted with CDC's assistance was not designed to address this question. This question is being pursued by Dr. Malcolm Smith at the National Cancer Institute and Dr. Les Robison at the University of Minnesota Cancer Center.

5. Did the *2002 Gene, Environment, and Childhood Cancer Workshop* at the National Cancer Institute produce useful recommendations of which we should be aware? Were they any different than the recommendations provided by the Fallon expert panel assembled to review the Fallon cluster?

The Summary Minutes from the Workshop on Gene-Environment Interactions in the Etiology of Childhood Cancer:

> The Report of the Workgroup for the Gene-Environment Interactions in the Etiology of Childhood Cancer explained that despite a multitude of epidemiologic studies over several decades, the causes of childhood malignancies are poorly understood. In very broad based and somewhat ambitious recommendations, the workgroup stated that epidemiological studies are "needed to assess the independent and combined effects of maternal preconception body mass, pregnancy weight, diet, physical activity, hormonal profiles, immune function, smoking, alcohol use, and diabetes with the offspring's birth weight, infant feeding, and genetic variants in one-carbon metabolism, insulin-related, hormonal, and immune pathways. Epidemiological studies were recommended to assess the interactions of certain occupational and environmental exposures with specific genetic pathways in the etiology of childhood cancers. Hypotheses for further evaluation include the role and timing of novel or common variant infectious agents in the relation to the genetically-influenced immune response and other exposures in occurrences in childhood malignancies."
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> "Populations deserving enhanced surveillance or perhaps full-scale epidemiologic study include: children exposed to known carcinogens, otherwise healthy children carrying cytogenetically abnormal lymphocytes characteristic of pediatric leukemia, **and populations with unusual occurrence of specific types of childhood cancer...** Workgroup participants also called for methodological studies to: improve exposure assessment, evaluate alternatives for control groups, incorporate cross-disciplinary approaches to quantify exposures more accurately, and pool childhood cancer data internationally to broaden the range and diversity of exposure levels. Reference data describing the range of values in healthy children's diets, physical activity levels and growth, as well as in their household, school and other environments are needed to help identify the upper and lower limits for risk factors in childhood cancer."

The report of the Fallon Expert Panel was probably not quite as ambitious and far-reaching as the above mentioned report of the Workshop on Gene-Environment Interactions in the Etiology of Childhood Cancer. Whereas the above mentioned report suggested that populations with an unusual occurrence of specific types of childhood cancer deserved, at the very least, enhanced surveillance, full-scale epidemiologic study might also be indicated. The recommendations from the Expert Panel for Fallon focused more on enhanced surveillance, biological sampling, and

exposure assessment. It was the feeling of the Fallon Expert Panel that a chemical exposure would probably not explain the ALL epidemic.

Questions About Cluster Investigation; Risk Management:

6. **Would it advance the understanding of leukemogens to ask affected families in Sierra Vista to provide biologic or environmental samples now? Or, is there another way that our participation in a larger, multi-site study might assist in such understanding?**

In an ideal study designed to look at that question, case children would have been enrolled in a pediatric oncology protocol from diagnosis, and prior to treatment, thus blood and bone marrow samples would have been taken and available for study at a later date. After treatment has begun, samples may not be of optimal value. In terms of asking families to provide samples at this time, this would make sense if there was evidence of an environmental exposure that was of concern. However, in Sierra Vista, it appears that an environmental study was conducted in air, water, and soil, and no exposures were identified which would be considered to be a health concern.

In addition, the number of children diagnosed with leukemia, although a tragedy for each family, is still fairly small and may not in fact constitute an elevated rate or true "cluster." We have, on multiple occasions, stated and would like to reiterate our willingness to collect biological samples for analysis and/or storage for future use. Although these may not be of value to the affected Sierra Vista families, the samples may contribute to future research efforts.

7. **The CDC has recently reviewed the literature concerning the causes of leukemia. Is the CDC aware of specific steps or actions that ADHS should recommend to reduce the risk of leukemia to children? ....to relatives?**

Based on the results of environmental studies to date by the Arizona Department of Health Services, no common environmental exposures were identified in air, water, or soil that might have placed residents of the Sierra Vista area at greater risk of developing leukemia. In our study on childhood leukemia in Churchill County, Nevada, the extensive investigation of environmental exposure and potential associations with childhood leukemia, no specific environmental exposures were identified that were linked to the elevation in childhood leukemia rates, nor were there any specific steps or actions taken that ADHS could recommend to reduce the risk of leukemia to children or their relatives. The recommendation to reduce consumption of community water in Churchill County, Nevada, due to high levels of arsenic, was made to address other potential health concerns. The evidence does not suggest that arsenic was related to the development of leukemia. Unfortunately, at this time, the science underlying our understanding of the etiology of childhood leukemia is not sufficient to explain the cause of the epidemic, or to identify any specific steps to reduce the risk of leukemia in children.